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DRUG TREATMENT OF HYPERTENSION

A series of appraisals of the various types of drugs used in the treatment of hypertension will appear in future issues of The Medical Letter. The following statement introduces the series.

A large and steadily growing number of drugs are offered for the treatment of primary (essential) diastolic hypertension, most of them intended to lower the increased peripheral vascular resistance characterizing the disorder. But the factors that initiate and maintain increased peripheral resistance are unknown.

Since stimulation of the sympathetic nervous system increases vasopressor responses, it might be supposed that hyperactivity in these nerve pathways is at least a connecting link in the chain of causes; but continuous hyperactivity of the sympathetic nervous system is not present in primary hypertensive disease, and cannot be the cause of hypertension. Indeed, the sympathetic nervous system may actually be hypoactive in some instances. Nevertheless, blood pressure can be lowered by inhibiting sympathetic activity and reducing it below normal — and it is this effect that the majority of present-day therapeutic agents are intended to achieve.

NON-PHYSIOLOGIC TREATMENT - Other drugs, such as the thiazide diuretics, work primarily by decreasing extracellular fluid volume, even though the volume is probably not abnormally elevated in primary hypertension. Thus, drug therapy of hypertension does not correct whatever physiologic defects are responsible for the disorder. Although this limitation does not prevent effective use of drugs in many patients, one must be aware that these drugs are hypotensive and palliative — rather than antihypertension — agents.

Besides the lack of knowledge of basic causes, the drug treatment of primary hypertension is complicated by the fact that all available hypotensive agents produce symptoms and toxic effects, some of them serious. Moreover, these undesirable effects are often inherent in the therapeutic action of the drug. For instance, with the sympatholytic drugs, orthostatic hypotension is not a "side effect"; when the drugs inhibit sympathetic nervous system activity they unavoidably prevent the adjustments to the upright position controlled by this system. Since available hypotensive therapy is palliative and all hypotensive drugs can produce unwanted effects, it becomes important to know whether reduction of

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the blood pressure is likely to retard the progression of the disease and improve the life expectancy of the patient. In the accelerated ("malignant") form of hypertension the accumulated evidence indicates that longevity is increased and deterioration of renal function delayed. In the less severe forms of diastolic hypertension, the available evidence favoring the use of drugs is considerably more debatable.

OTHER FACTORS - Although diastolic blood pressure levels consistently above 130 to 140 mm. Hg usually indicate severe and progressive hypertensive disease which should probably be treated, blood pressure alone is not reliable prognostically; it must be considered along with such other factors as sex, age, and cardiac, renal and retinal status. It is also well established that blood pressure is often labile, that it is subject to marked variation produced by nonpharmacologic stimuli, and that noxious stimuli may continue to produce pressor responses even when basal diastolic blood pressures are lowered by drugs.

In the selection of a drug, the physician's problem is further complicated by the fact that trials of hypotensive drugs are often performed without rigid criteria of control, and do not provide valid data about actual pharmacologic effects. When drugs are prescribed, irregular administration and absorption add further difficulties, so that even under favorable circumstances, a uniformly maintained reduction of blood pressure is not often achieved.

ACCELERATED HYPERTENSION - Despite all such considerations, however, attempts to lower blood pressure are well justified in the accelerated form of hypertension. In less severe diastolic hypertension and in "aortic" systolic hypertension the nonphysiologic character of drug treatment and the therapeutic risks of the various drugs assume considerable importance, particularly when the hypertension is asymptomatic and is so mild that it does not inconvenience the patient.

In such cases, the factors other than blood pressure which influence prognosis must be given due attention. For instance, a sedative, or no drug at all, might be indicated in a hypertensive middle-aged woman with no symptoms and no evidence of cardiac or renal impairment; in a young male patient, the same clinical findings might call for the use of a ganglionic blocking agent, even though it might convert his disease from an asymptomatic untreated disorder to a disorder characterized by symptoms of the treatment.

The drugs offered for the treatment of hypertension can be divided into several groups depending on their site of action, and discussions of each of these groups will be presented in future issues.

NISENTIL

Alphaprodine (Nisentil — Roche) is a piperidine compound chemically similar to meperidine (Demerol — Winthrop). Because it is claimed to provide more rapid onset and shorter duration of action than other narcotics, the manufacturer recommends its use in obstetrics, prior to cystoscopy, bronchoscopy,

and operative dentistry, and as a narcotic supplement to general and regional anesthesia. Nisentil is without doubt an effective analgesic; but its claimed advantages over other potent analgesics are difficult to judge on the basis of available studies.

As early as 1948 the compound was demonstrated to have analgesic effects comparable to those of morphine in experimental pain in man, but there have been no adequately controlled studies in pathological pain to show how it compares with morphine or Demerol in analgesic potency, and whether in equipotent doses it has greater rapidity of onset and shorter duration of action. And except in terms of equivalent analgesic potency, the manufacturer's claims of less respiratory depression than with morphine and of the rarity of nausea, vomiting, restlessness and confusion have little meaning.

In one study in man (L. R. Orkin, et al., Anesthesiology, 16:699, 1955) 60 mg. of the drug administered subcutaneously depressed respiration as much as 100 mg. of Demerol intravenously. [Respiratory depression is promptly antagonized by nalorphine (Nalline — Merck) or by levallorphan (Lorfan — Roche).] The drug also produced all of the other undesirable effects of morphine and related potent analgesics. These included nausea, vomiting, dizziness, itching, sweating, development of tolerance and addiction. Its addiction liability is similar to that of Demerol.

IN OBSTETRICS - Because of its reported short action, there have been numerous trials of Nisentil, most of them uncontrolled, in obstetrics. The reports on these trials have been uniformly enthusiastic, even though nausea, vomiting, dizziness, and decreased uterine contractions (affecting 10 per cent of the patients in one study) occurred in mothers, and respiratory depression occurred in the babies. In the only reported double-blind study in obstetrics (J. S. Gilliam, et al., Am. J. Obst. and Gyn., 75:1105, 1958) Nisentil produced significantly more neonatal asphyxia (7.6 per cent) than did Demerol (2.5 per cent), but it also produced significantly less vomiting.

The manufacturer suggests in his package insert that combinations of Nisentil and Lorfan in a 50:1 ratio will prevent respiratory depression without interfering with analgesia. There is no satisfactory evidence to support this claim and little basis for the clinical use of mixtures of narcotics and narcotic antagonists (J. Telford and A. S. Keats, Anesthesiology, 22:465, 1961).

If Nisentil does in fact prove to be shorter acting than morphine or meperidine at equivalent analgesic doses, it may have particular usefulness in the special situations suggested by the manufacturer. Apart from shorter action, Nisentil appears to have no advantages over other narcotics.

Nisentil is marketed in 1-cc. ampules containing either 40 mg. or 60 mg. of the drug and in 10-cc. multiple-dose vials which contain 60 mg. per cc. The dose currently recommended by the manufacturer is 40 to 60 mg. subcutaneously or 20 to 30 mg. intravenously. The cost of 60 mg. of Nisentil is about twice that of 100 mg. of Demerol which in turn is more than twice that of 15 mg. of morphine.

SYSTEMIC FLUORIDE FOR PREVENTION OF DENTAL CARIES

One of the most important public health measures of recent years is the fluoridation of public water supplies. In communities where fluoridation has been introduced, the incidence of dental caries in children has been cut by as much as 60 per cent. The greatest effect is obtained when fluoride is continuously available before the tooth mineral is deposited; therefore, maximum benefits appear in children whose mothers drank fluoridated water during pregnancy and who have themselves had fluoridated water since birth. Older children benefit to a lesser degree.

In communities where the water is not treated, the benefits of fluoridation can be obtained from daily oral supplements of sodium fluoride (not calcium fluoride), available either as tablets or as liquid drops (Karidium — Lorvic; Luride — Hoyt; and others). Supplementation is best started by the mother in the fourth month of pregnancy, when the teeth are beginning to form.

DOSAGE - Where the water has little or no natural fluoride, enough sodium fluoride to provide 1 mg. of fluoride ion should be taken daily. This amount is obtained from a single Karidium or Luride tablet, or from an appropriate number of drops of the liquid in drinking water or fruit juice. The fluoride can either be given as a single daily dose, or it can be added to the amount of drinking water the child will take during the day. Or 1 mg. can be added to each quart of water (equal to one part per million) used for the family's drinking and cooking.

The single daily dose insures ingestion of an adequate amount of fluoride each day, but provides the entire amount at once. The addition of fluoride to the drinking and cooking water provides continued ingestion of smaller amounts during the course of a day, as with a fluoridated water supply; but the daily dose is more difficult to control, particularly when not all food and drink are consumed at home. Which method is superior is not known.

Excessive amounts of fluoride may cause brown mottling of the enamel (dental fluorosis), and in very great excess, fluoride may produce skeletal fluorosis with abnormally high bone density. But when the ingested fluoride is of the order of 1 mg. per day, no fluorosis occurs. Some preparations provide sodium fluoride along with vitamin D and ascorbic acid (Enziflur — Ayerst, and Funda-Vite(F) — Hoyt), and other vitamins (Quanti-Vite(F) — Hoyt); however, it is more rational and safer to prescribe vitamins separately.

TOPICAL FLUORIDES - Although it is well established that systemic fluoride produces a much greater reduction of caries than topical fluoride, the semiannual topical application by a dentist of stannous fluoride to children's teeth does provide some protection against caries. The usefulness of dentifrices containing fluoride still remains to be definitely established; they may, however, effect some reduction in the incidence of caries, as indicated by the provisional acceptance given to one fluoride toothpaste (Crest) by the Council on Dental Therapeutics of the American Dental Association. (When prescribed in quantities of a hundred, the cost of Karidium or Luride to the patient is about 2 to 2 1/2 cents per tablet.)

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